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THE EFFECT OF SYMPATHOMIMETIC AMINES ON RADIATION-INDUCED TOLERANCE TO PENTOBARBITAL IN THE RAT

ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Atomic Support Agency
Bethesda, Maryland

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THE EFFECT OF SYMPATHOMIMETIC AMINES ON RADIATION-INDUCED TOLERANCE TO PENTOBARBITAL IN THE RAT

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FOREWORD
(Nontechnical summary)

Low doses of radiation are known to increase the normal background electrical activity of the nervous system of animals. This intensified activity generally results in an increased release of a chemical substance (neurotransmitter) from the nerve. Mice receiving sublethal doses of radiation have been shown to respond less to pentobarbital than unirradiated control animals. This increased tolerance of mice to pentobarbital appears related to the increased release of neurotransmitter. The present study examines this relationship in rats using x radiation and drugs known to effect the release of neurotransmitter.

Male rats were given 250-, 500-, or 1000-rad midline tissue doses of 300 kVp x rays. Twenty-four hours after irradiation, the rats of all groups were infused with sodium pentobarbital at a constant rate until respiration ceased. The amount of pentobarbital needed to reach this end point was determined and the mean value of each group was statistically compared with that of an unirradiated control group. Reserpine treatment and/or amphetamine treatment were given to other groups of irradiated and unirradiated rats and pentobarbital toxicity similarly measured in these animals.

Increased tolerance (amount of drug necessary to stop respiration) to sodium pentobarbital was observed in the rats after 500- or 1000-rad doses, but not in the rats receiving 250 rads. A similar increased tolerance was seen in amphetamine-treated unirradiated rats. Animals receiving reserpine alone or in combination with amphetamine and/or radiation, had essentially the same pentobarbital tolerance as

control animals. Furthermore, amphetamine administration eliminated the increased tolerance ordinarily seen 24 hours after 1000 rads of x rays.

The results indicate that the neurotransmitter norepinephrine plays some role in the increased pentobarbital tolerance of rats observed after irradiation.

ABSTRACT

Male Sprague-Dawley rats were given 250-, 500-, or 1000-rad midline tissue doses of 300 kVp x rays. Twenty-four hours postirradiation the acute toxicity of sodium pentobarbital was determined in these animals. Rats receiving 500 and 1000 rads demonstrated an increased tolerance to sodium pentobarbital, but no change in toxicity was observed in animals given 250 rads. This radiation-induced increase in pentobarbital tolerance was similar in degree to that observed in unirradiated rats treated with amphetamine, a known barbiturate antagonist. However, when rats received amphetamine as well as 1000 rads of x rays no increased tolerance to sodium pentobarbital was observed. Four days of reserpine treatment prior to irradiation also abolished the radiation-induced increase in sodium pentobarbital tolerance. These results suggest that increased central norepinephrine levels are responsible for the radiation-induced increase in tolerance to pentobarbital.

I. INTRODUCTION

Sublethal doses of radiation have been shown to increase the electrical background activity of the central nervous system (CNS).[3,4,6] Barnes reported that 102 R of x rays enhanced pentobarbital tolerance in mice.[1] He suggested that this radiation-induced increase in tolerance to pentobarbital is due to facilitated CNS electrical activity antagonizing barbiturate depression.

Under normal physiologic conditions facilitated CNS electrical transmissions would result in an increased release of central neurotransmitter. If radiation increases tolerance to pentobarbital by facilitating electrical activity, then drugs which increase the release rate of or deplete stored quantities of central neurotransmitter should modify radiation-induced changes in pentobarbital toxicity. The ability of irradiated rats to tolerate pentobarbital was measured after treatment with amphetamine and/or reserpine to test this hypothesis.

II. PROCEDURE

Male Sprague-Dawley rats* (250-300 grams) were housed one per cage in an environmental controlled room and acclimated for a minimum of 1 week.

Rats were bilaterally irradiated using an x-ray machine and the following exposure factors: 300 kVp, 20 mA, HVL 1.5 mm Cu, and source to animal center line distance of 50 cm. The animals were placed in rectangular Plexiglas boxes and two rats were irradiated at the same time (Figure 1). Depth-dose measurements made in cylindrical Plexiglas rat phantoms using miniature tissue-equivalent ionization chambers[2] showed that the maximum to minimum dose ratio through the phantom

* Environmental Control Co., Washington, D. C.

was 1.09 indicating that the exposures were Class A.[7] The dose rate at the midline of the phantom was 129 rads per minute. Groups of rats received midline tissue doses of 250, 500, or 1000 rads.

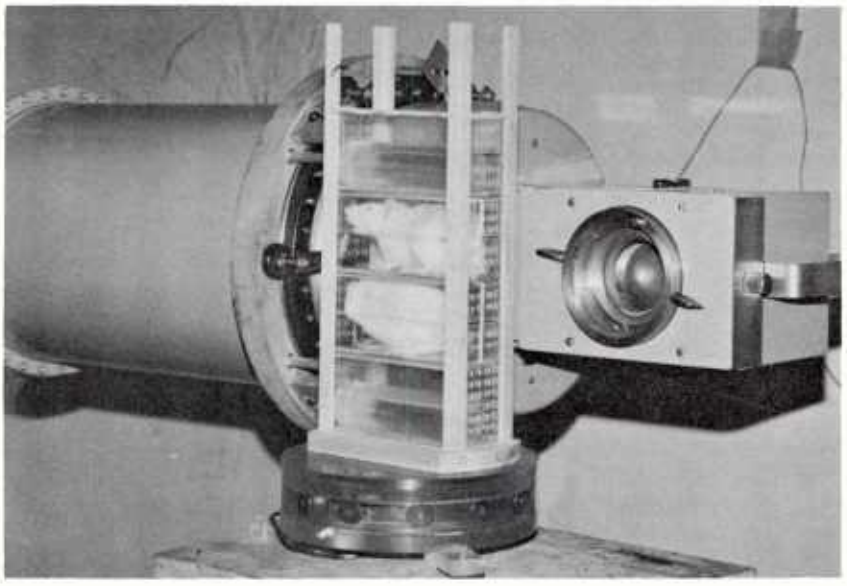

Figure 1. X-ray exposure array for rats

Sodium pentobarbital acute toxicity was determined 24 hours after the animals were irradiated. Control, fasted control, and irradiated animals were lightly anesthetized with ether and the tail vein catheterized using a 23-gauge needle attached to polyethylene tubing (i.d. 0.011", o.d. 0.024"). The rats were then confined in Plexiglas cylinders and allowed to recover from the anesthesia. Pentobarbital was infused via the polyethylene tubing at a constant rate of 2.95 mg min^{-1} (0.116 ml of solution min^{-1}) using an infusion pump. The assembled apparatus is shown in Figure 2. The end point of acute toxicity for pentobarbital in the animal was the cessation of respiration. The amount of pentobarbital required to achieve this end point was calculated as milligrams per kilogram of body weight.

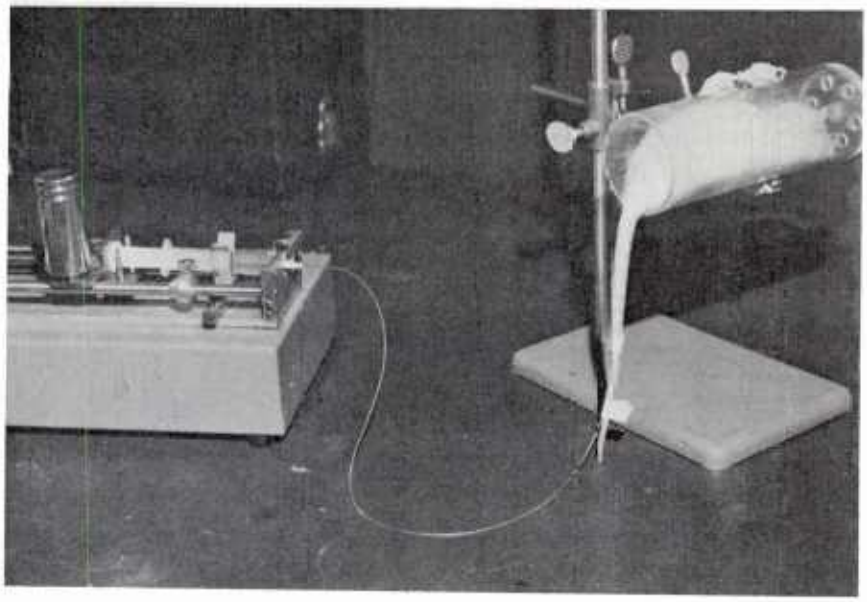

Figure 2. Setup for infusion of rats

The effect of amphetamine sulfate on pentobarbital toxicity was determined in irradiated (24 hours after 1000 rads) and in unirradiated rats. Amphetamine (8 mg kg^{-1}) was administered intraperitoneally 1/2 hour prior to pentobarbital infusion (a time sufficient to insure the onset of drug activity as indicated by restlessness, agitation, and increased motor activity of the animals). The effect of preirradiation reserpine treatment (0.1 mg kg^{-1} day^{-1} intramuscularly for 4 days) on pentobarbital acute toxicity was tested in irradiated (24 hours after 1000 rads) and in unirradiated rats. The same regimen of reserpine treatment was tested in conjunction with amphetamine given 1/2 hour prior to pentobarbital infusion in irradiated (24 hours after 1000 rads) and in unirradiated rats.

Differences between the mean values of the test groups were evaluated for statistical significance using Student's "t" test.

III. RESULTS

Table I summarizes the results. Rats demonstrated an increased pentobarbital tolerance 24 hours after receiving 500 and 1000 rads, but not after 250 rads. Fasting unirradiated rats for 48 hours had no effect on pentobarbital tolerance.

Unirradiated, amphetamine-treated rats demonstrated an increased ability to tolerate pentobarbital. When amphetamine was administered to animals 24 hours after a 1000-rad dose, however, a decrease in pentobarbital tolerance was observed; this decrease was not significant at the 0.05 level of probability.

Four days of reserpine treatment abolished the increased tolerance to pentobarbital in unirradiated amphetamine-treated rats as well as in irradiated rats.

Table I. The Effects of X Ray, Amphetamine and Reserpine Administration on Pentobarbital Acute Toxicity in the Rat

Regimen	Number of rats	Toxic dose of pentobarbital mg kg^{-1} ± S. E.
Control	29	87.2 ± 5.5
Control, fasted 48 h	12	85.7 ± 5.2
Irradiated (24 h after 250 rads)	15	85.6 ± 4.8
Irradiated (24 h after 500 rads)	12	*107.6 ± 5.4
Irradiated (24 h after 1000 rads)	12	*106.3 ± 3.5
Amphetamine treated	21	*105.7 ± 4.8
Amphetamine treated (24 h after 1000 rads)	18	76.5 ± 5.0
Reserpine treated	7	85.9 ± 7.1
Reserpine and Amphetamine treated	9	91.2 ± 4.8
Reserpine treated (24 h after 1000 rads)	10	91.1 ± 5.9
Reserpine and Amphetamine treated (24 h after 1000 rads)	11	84.7 ± 2.9

* $p < 0.05$ (treatment group compared with control group)

IV. DISCUSSION

Five hundred- and 1000-rad whole-body doses of x rays were antagonistic to the depressant action of pentobarbital on the CNS of the rat; however, no such effect resulted from a dose of 250 rads. The increased ability to tolerate pentobarbital was not due to inappetence of the animals since unirradiated rats fasted for 48 hours did not show any change in pentobarbital tolerance as compared to fed control animals. The increased central neuronal activity suggested by the data from this study appears to confirm the reported increase in CNS electrical activity following exposure to radiation.

In situations of stress, the immediate physiologic response of the animal is attempted restoration of homeostasis. A large facilitatory input from the peripheral organs is transmitted to the reticular activating system which in turn increases the electrical activity of nearly all parts of the CNS to accomplish this restoration.[5] Increased bioelectrical activity would result in an increased release of central neurotransmitters, particularly in the important respiratory and vasomotor centers located in the midbrain. Chief of these neurotransmitters is norepinephrine which is normally found in high concentrations throughout this region of the CNS.[8]

Reserpine and amphetamine were studied in various combinations with pentobarbital and irradiation. Both drugs act centrally by increasing the release of norepinephrine.[8] Amphetamine's well-known antagonism to pentobarbital was observed as a decreased pentobarbital toxicity in unirradiated animals. This decreased pentobarbital toxicity appeared similar to that observed following irradiation. However, irradiated rats treated with amphetamine appeared to have a decreased tolerance

to pentobarbital, 24 hours postexposure (1000 rads), as compared to control animals (the decrease was not statistically significant in this experiment). From these data, it appears that when x radiation and amphetamine treatment are combined the ability of each to counteract CNS pentobarbital depression is lost. It is difficult to explain why the combination of amphetamine and irradiation does not increase pentobarbital tolerance when each used singly does. It is possible that the combination of amphetamine and irradiation exceeds a maximum limit after which central neuronal facilitation is reflectively inhibited or intoxicated.

Reserpine is an intraneuronal depletor of norepinephrine. Reserpinization abolished the increased tolerance of irradiated animals to pentobarbital. This observation further implicates central norepinephrine in the decreased pentobarbital toxicity caused by x irradiation. Similar effects of reserpinization on pentobarbital toxicity were observed in amphetamine-treated rats.

The findings of this study indicate that 500 and 1000 rads of x rays increased the rat's ability to tolerate pentobarbital. This increased tolerance appeared similar to that obtained using amphetamine, a known pentobarbital antagonist. Two hundred and fifty rads of radiation failed to increase pentobarbital tolerance indicating a threshold dose of radiation is necessary to elicit this response. The radiation-induced increase in pentobarbital tolerance is abolished by reserpine treatment or by combining amphetamine treatment with irradiation.

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